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Summary: Workshop on Health Risks Attributable to ETS Exposure in the Workplace

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This article is an overall summary of all presentations and discussions from the Workshop on Environmental Tobacco Smoke Risk Assessment held 9-10 July 1998 in Baltimore, Maryland.

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This 1998 workshop was convened to address the health risks of exposure to environmental tobacco smoke (ETS) in the workplace. It was paired with a 1997 workshop on issues related to ETS exposure in work environments (1). In the 1998 workshop, a multidisciplinary group of participants was charged with reviewing evidence on the quantitative risks to health posed by ETS and to discuss development of risk assessment methodology for the future. The overall charges for the present workshop were

- to consider various health outcomes and make recommendations regarding those health outcomes to be included in assessment of health risk resulting from ETS in the workplace;
- to consider available studies addressing these health outcomes and to evaluate the validity of data for estimating risk from occupational ETS exposure;
- to review and evaluate mathematical models useful for estimating the risk due to ETS exposure;
- to examine dose-response models and to characterize the models regarding validity and uncertainty in estimating health risk attributable to ETS exposure in the workplace.

The 1997 workshop evaluated the accuracy of exposure measurement methods for ETS and the utility of various smoke constituents as surrogates for measuring ETS exposure; it also reviewed and

evaluated mathematical models for predicting ETS concentrations (2). In their overall conclusions, the workshop participants set out a general approach for estimating the distribution of ETS exposure in the United States (2). For a quantitative risk assessment to be conducted, information on the ETS exposure distribution should be combined with estimates of the exposure-effect relationships for the health effects of interest (3). The Occupational Safety and Health Administration had followed a similar type of general approach in its risk assessment in 1994 of selected risks from ETS exposure in the workplace (4).

The evidence on adverse effects of ETS has steadily increased over recent decades (5). For adults--the focus of this workshop--causal associations have now been identified between ETS exposure and lung cancer (6-10) and also between ETS exposure and ischemic heart disease (9-11). Some data indicate other adverse effects of ETS in adults, including increased risk for asthma and respiratory symptoms and reduced lung function level (5), but there is not yet enough evidence to reach conclusions concerning causality. Other health effects linked to ETS exposure of adults include low birth weight and increased risk for some nonrespiratory cancers (5,9). This workshop was primarily concerned with four health outcomes. Heart disease and lung cancer were included because a hazard has been identified. Asthma was considered because of its high prevalence and the known responsiveness of persons with asthma to inhaled pollutants. The exposure of pregnant women was addressed because of the potential vulnerability of the fetus.

The charges given to workshop participants in relation to the four health outcomes are listed in Table 1. Workshop participants were also asked to address key methodologic issues that arise in interpreting the epidemiologic data on ETS exposure and in summarizing these data with meta-analysis. Confounding has been of particular concern, as exposure to ETS is now associated with lifestyle risk factors in some populations.

Table 1. Charges for the specific health outcomes.

Exposure assessment	<p>What are important exposure assessment issues for health risk assessment based on human studies of workplace ETS exposure?</p> <p>Are there data available on markers of ETS exposure in the workplace?</p> <p>Are there data on comparative levels of ETS exposure at home and work to support extrapolation from studies of spousal smoking?</p>
Cardiovascular disease	<p>Has workplace exposure to ETS been investigated as a risk factor for coronary heart disease and other cardiovascular diseases?</p> <p>Are quantitative risk estimates available?</p> <p>Can the data on spouse smoking and coronary heart disease risk be extended to workplace exposure?</p> <p>Does the 'healthy worker effect' have an impact on estimates of cardiovascular disease risks arising from workplace ETS exposure?</p> <p>Are there risk estimates that control for potential bias due to <i>a</i>) misclassification of smoking status (some reported nonsmokers are actually smokers; and <i>b</i>) confounding by lifestyle, e.g., diet and exercise?</p> <p>Are there data available on biologically plausible mechanisms?</p>
Lung cancer	<p>Are risk estimates available for workplace exposure? What is the precision of such estimates? What are the sources of uncertainty in extending them to current levels of exposure?</p> <p>Can the evidence on risks associated with spouse smoking be extended to the workplace?</p> <p>Are there any models of carcinogenesis useful for estimating workplace risks of ETS exposure?</p>
Asthma	<p>Are there data supporting a role for ETS in causing asthma in adults? Are there data available related to workplace exposure?</p>

	Has ETS exposure been shown to exacerbate asthma in adults? What are the findings of exposure of volunteers with asthma to ETS? Are there epidemiologic data available on this issue?
Low birth weight	What is the dose-response relationship for ETS exposure and low birth weight? Are exposures in the workplace in a range of biologic concern? Are there studies of occupational exposure to ETS and birth weight? Can results from studies of birth weight and ETS exposure generally be extended to the workplace?

Meta-analysis--combining summary estimates from individual studies--has been used to evaluate the hazard posed by ETS and to quantitatively estimate the increased risk associated with exposure. Questions have been raised concerning the use of meta-analysis generally and more specifically regarding its application to studies of ETS. This general topic was also included in the scope of the workshop.

In this article we synthesize the information presented in the workshop presentations and in the related discussion. There was no attempt to achieve group consensus on all issues; consequently this summary should not be construed as necessarily reflecting the views of all participants. The peer-reviewed articles in this monograph are based on presentations at this workshop. These papers as well as the other presentations are summarized in the following sections.

Exposure Assessment for the Purposes of Health Risk Assessment

The bridge from ETS exposure assessment issues to those of health risk assessment (3) was established at the outset of the workshop. Concepts of ETS exposure assessment relevant for health risk assessment based on human studies were presented and data on ETS exposure levels in workplaces and residences were reviewed. The sources of variation in exposure, dose, and biologically effective dose of ETS, as well as in individual susceptibility to the health effects, were discussed and a model to describe them was presented (3,12). A biologically driven approach to select the most appropriate ETS exposure assessment method for assessing health risk was proposed. Special reference was given to the diseases considered in the workshop. This approach accounts for the pathophysiology of the disease and the time specificity of exposure and combines this information with the time period that can be assessed with different exposure assessment methods. For example, an indicator of short-term exposure is appropriate in studies of asthma exacerbation, whereas an assessment of cumulative exposure is relevant for lung cancer.

The workshop emphasized that health risk assessment requires two types of exposure assessment. First, an unbiased estimate of the exposure-effect relation between ETS and the health effect is needed, derived from health effects studies that meet criteria for quality; meta-analysis or pooled analysis can be used to combine data from several studies. Estimates of these relationships were the topic of this workshop. Second, estimates of the distribution of ETS levels in the workplaces are needed if the occupational hazard due to workplace ETS is the focus of the risk assessment. These estimates were the focus of the 1997 workshop.

There is no biologic or scientific basis for expecting that the effects of ETS exposure in the workplace would differ from the effects related to home ETS exposure if the exposure is of equal magnitude. Workplace exposures likely are more variable than residential exposures because of larger variability in a) the size and ventilation characteristics of workspaces, b) the number of smoking co-workers, and c) smoking policies in different workplaces. However, median and mean indoor air

concentrations of ETS markers, especially nicotine and respirable suspended particles, have been found to be essentially comparable between workplace and residential environments in the United States as well as in other countries (3,8,13,14). Some work forces, however, such as hospitality workers, may be exposed to high levels of ETS that are rarely encountered in residential settings.

Also at issue was how questionnaire-based risk estimates should be combined with ETS marker measurements used to assess the exposure distribution when assessing the proportion of disease cases attributable to workplace ETS exposure. Some estimates of the relationship between questionnaire-based assessment of exposure and indoor ETS marker concentrations have been provided by experimental and field studies (15-19). More research is recommended, however, to achieve more precise estimates of these relationships under different environmental conditions.

Cardiovascular Diseases

The charges concerning cardiovascular diseases were broad (Table 1). The evidence on spouse's smoking and heart diseases as well as the studies of workplace exposure in particular were reviewed and key methodologic questions including study population selection, exposure misclassification and confounding were addressed. In addition, data on biologic mechanisms were discussed. Usefulness of meta-analysis in estimating coronary heart disease risk from workplace ETS exposure and possibilities to model exposure-effect relationships were also addressed.

Chappell (20) presented a thorough discussion on the use of meta-analysis in estimating coronary heart disease risk from workplace ETS exposure. Advantages as well as potential problems in applying this analytical technique to the available data were discussed. Further suggestions on how to improve the quality of the risk estimates by adjusting for duration and intensity of exposure to better reflect workplace conditions were offered. As an alternative to meta-analysis for estimating occupational risk, Chappell also suggested the use of a stochastic approach where distributional information based on the available studies rather than simply on point estimates is considered.

The relationship of ETS exposure to subclinical measures of the development of atherosclerotic disease was addressed in a separate presentation. B-mode real-time ultrasound can be used to estimate the extent of atherosclerosis noninvasively, offering the possibility of measuring subclinical markers of disease; the intimal-media thickness of the carotid artery has been used as an index of systemic atherosclerosis. Howard and Wagenknecht (21) described cross-sectional and longitudinal findings from the Atherosclerosis Risk in Communities (ARIC) study, which linked ETS exposure to both greater thickness and an accelerated rate of increase in thickness of the intimal-media. This finding implies that ETS exposure accelerates the process of atherosclerosis. Other measures of subclinical disease considered in relation to ETS exposure included decreased endothelial function and silent cerebral infarction.

Several presentations covered the evidence on ETS exposure and heart disease risk. Thun and colleagues (22) carried out a meta-analysis of 17 studies, 9 cohort and 8 case-control, on the risk of ischemic heart disease for nonsmokers married to smokers. The evidence, which encompassed more than 485,000 lifelong nonsmokers and 7,345 events, was substantially more extensive than 5 years earlier when the Occupational Safety and Health Administration conducted its risk assessment, using the estimate from only one study conducted in Washington County, Maryland (23). The meta-analysis provided an overall estimate of relative risk of 1.25 (95% confidence interval [CI], 1.17-1.33).

Together, Thun and Howard (24) considered the various types of bias considered to be potential

explanations for the association of ETS with ischemic heart disease. These primarily include confounding and information bias. There has been concern that bias may at least partially explain the association because the relative risk has been considered disproportionately elevated in relation to relative risk values for active smoking. Their analysis indicated that the association cannot be readily explained by bias. Additionally, they described effects of acute exposure to ETS that provide insight concerning mechanisms that may underlie the association of ETS with cardiovascular disease.

Information available on risk attributable to workplace exposure was specifically addressed in two presentations. Kawachi and Colditz (25) summarized the available evidence from 5 studies, 3 case-control and 2 cohort. The point estimates of relative risk in the individual studies ranged from 1.2 to 1.9, but none of the estimates were statistically significant. It was stated that because of the imprecision of the risk estimates in all but one study, a modest increase in cardiovascular disease risk from workplace exposure to ETS could not be excluded. Additionally, in contrast to the evidence on spousal exposure to ETS and increased risk of cardiovascular disease, studies of workplace ETS exposure are still sparse and further research is needed. Steenland (26) set out an approach for conducting a quantitative risk assessment of workplace ETS. His approach uses a relative risk estimate derived by meta-analysis. This method leads to an estimate of approximately 340 excess ischemic heart disease deaths per year among nonsmoking U.S. workers age 35 to 70 years.

Lung Cancer

A causal role of ETS in induction of lung cancer is strongly established (7,8). Biologic plausibility is derived from the fact that ETS contains the same carcinogenic compounds as mainstream smoke inhaled by active smokers. The workshop charges on workplace ETS exposure and lung cancer included a review of estimates of lung cancer risk associated with ETS exposure, with emphasis on workplace ETS exposure. Several contributors reviewed potential sources of bias and confounding in studies of ETS and lung cancer as well as the methods that have been applied in the studies to reduce their impact. Finally, different modeling approaches to assess the lung cancer risk related to workplace ETS exposure were reviewed.

Over 40 studies have examined the relationship between spousal smoking and risk of lung cancer. Many of them have provided evidence of an exposure-response relationship with the number of cigarettes smoked by the spouse and/or with the duration of ETS exposure at home or in the workplace (27,28). The risk related specifically to workplace ETS exposure has been studied in women in 16 hospital-based or population-based case-control studies and in men in 7 hospital-based or community-based case-control studies and in 1 cohort study (28,29). Most of the studies were not explicitly designed to evaluate the association between workplace ETS and lung cancer risk and consequently had low power to detect a statistically significant relationship (28). In general, the risk estimates appear to be consistent with those for exposure from a smoking spouse. Recent studies have had larger sample sizes and addressed many of the potential sources of bias. These studies have shown a statistically significant increase in lung cancer risk related to workplace ETS and have provided evidence of increasing risk with increasing duration of workplace ETS exposure (30-33).

A pooled analysis or meta-analysis of individual studies can provide a useful approach to combine data from small, individual studies to assess the risk. A meta-analysis is often a more feasible approach, but it does not provide an opportunity to assess heterogeneity of risk within subgroups, whereas a pooled analysis of raw data from studies usually offers greater flexibility in modeling (34). Approaches to use the relatively large body of data on the exposure-response relationship between lung cancer risk and spouse's smoking to assess risk related to workplace ETS were discussed

(34,35). The exposure-response relationship between lung cancer and ETS exposure due to spousal smoking among nonsmoking women, using the number of cigarettes smoked by the husband as an indicator for the amount of exposure, was evaluated using a log-linear model by Brown (35). A total of 14 studies contributed data to this analysis. The model for all countries combined predicted an excess risk of lung cancer of 17% per 10 cigarettes/day (95% CI, 12-22%), and the excess risk from the United States alone was 13% per 10 cigarettes/day (95% CI, 5-21%). On the basis of data on smoking habits in the two large cancer prevention studies by the American Cancer Society (36,37), the average number of cigarettes smoked daily by U.S. men was about 24 (35). Applying this value to the model, the average excess risk of lung cancer in nonsmoking women due to spousal smoking was 33% (95% CI, 14-56%). According to serum cotinine measurements in a large national survey of the U.S. population (38), the workplace ETS exposure of nonsmoking women is on average 42% of the home exposure of nonsmoking women. This corresponds to an average exposure of 10 cigarettes/day (35). When this average workplace ETS exposure was used to assess the excess risk of lung cancer in nonsmoking women, an estimate of 13% was obtained. After adjustment of the estimate for ETS exposure in the reference group for sources other than the workplace exposure, the estimated excess risk is 19% (95% CI, 10-28%).

As alternative approaches, one can model lung cancer risk in current and former smokers and extrapolate the results to low levels corresponding to ETS exposures or one can model restricted data from light smokers (34). The latter approach is more directly applicable to the range of exposures comparable with typical ETS exposure settings. The modeling based on data in current and former smokers should first adjust for ETS exposure in the reference group so that the effect estimate is not diluted by increased risk among ETS exposed nonsmokers. The exposure-risk patterns from light active smoking models do not indicate a threshold level below which exposures would not be expected to increase the risk of lung cancer (34). Average ETS exposure in nonsmokers has been estimated to be the equivalent of actively smoking 0.1-2 cigarettes/day (8,34). The risk ratio for smoking 0.5 cigarettes/day ranges between 1.1 and 1.3 in models restricted to light smokers only (34). The risk estimate of lung cancer in relation to ETS exposure is surprisingly consistent regardless of whether the modeling approach uses data on active smoking and extrapolates the estimates to low levels or whether more direct data on passive smoking are used.

Potential biases that might affect the risk estimates from lung cancer studies were discussed extensively by workshop participants (28,29,39,40). Hospital-based case-control studies may be weakened by a selection bias if recruitment of cases or controls is related in some way to ETS exposure. In recent years, several population-based case-control studies have been conducted to avoid this type of bias (28). In epidemiologic studies, some degree of misclassification of exposure and of outcome is likely to occur. In many of the studies, ETS exposure was classified on the basis of smoking by the spouse only while not capturing exposure from other sources, although as adults people are usually exposed from multiple ETS sources, including workplace and social settings. Consequently, the reference category classified as unexposed may include persons who have experienced substantial ETS exposure, thus diluting the obtained risk estimates (39).

In case-control studies, use of proxy respondents (usually a family member) to give information on exposures for lung cancer cases who are very ill or deceased may lead to greater misclassification of ETS exposure among cases compared to controls (28,29). However, information on ETS exposure variables reported by surrogate respondents has been found to agree closely with that reported by the lung cancer cases themselves. Studies comparing results in total study populations with analysis limited to cases interviewed in person have shown essentially similar results (28,29).

Recall bias can affect risk estimates if cases (or surrogates) consider ETS exposure as a possible explanation for the disease (28). The U.S. multicenter case-control study included controls drawn from the general population and controls recruited among patients with primary colon carcinoma (41). The latter control group was expected to be searching for an explanation for their cancer in the same manner as lung cancer cases. The results were consistent in case-control comparisons regardless of the control group used.

Misclassification of self-reported smoking status is a concern, as some current and former smokers may report that they are never smokers and are at higher risk for lung cancer because of their smoking (39). The proportion of ever smokers (current or former smokers) misclassified as never smokers has been estimated to be small: 3-7% (8,27,42). On the basis of measurements of urinary cotinine with a cut-off point of 50 ng/mg creatinine to indicate active smoking, the proportion of active smokers among reported never smokers was between 3 and 5% (30,43). Most of the ever smokers misclassified as never smokers have quit smoking and had smoked fewer cigarettes than an average smoker (39). In addition, although smoking spouses tend to marry each other, this type of differential misclassification of the smoking status does not appear to be likely with respect to workplace ETS exposure.

Women nonsmokers living with smokers have been shown to differ from those living with nonsmokers with respect to such disease risk factors as lifestyle and socioeconomic status (40). Whether the same factors are associated with workplace ETS exposure is unclear. Most studies published since the mid-1980s have adjusted for important potential confounders, although the set of confounders has differed among the studies. Most have accounted for some indicator of socioeconomic status, which can be seen as a surrogate for many lifestyle factors, but the possibility of residual confounding exists. Several studies have adjusted for exposure to other occupational hazards and for dietary habits, including low fruit and vegetable consumption and high saturated fat intake, and have shown negligible confounding by these factors of the relationship between ETS exposure and lung cancer risk (27-29,35). Modification of effects of ETS by other occupational and indoor exposures has not been studied (29). Potential synergism between these exposures and ETS should be studied to evaluate whether ETS is especially harmful in the workplace.

Asthma

Strong evidence exists for a causal role for ETS in the development and exacerbation of asthma in children (8,9). However, there are only a few studies on ETS and adult asthma. For asthma, the charges for the workshop participants were to review data on the role of ETS in causing asthma in adults, with special emphasis on workplace exposure, and to review data on effects of ETS on exacerbation of asthma in both epidemiologic and controlled exposure studies (44).

Only four studies of ETS and adult onset asthma were identified (45-48). Two longitudinal, one case-control, and one crosssectional studies all indicated that the risk of adult asthma is increased in relation to ETS exposure in general and in some instances specifically in relation to workplace exposure. Some methodological problems of the studies were identified including potential recall bias of exposures and bias in selection of study subjects (44). Only one epidemiologic study had addressed the effects of ETS exposure on exacerbation of asthma in adults and found increased emergency room visits, hospitalizations, medication use, and absence from work among ETS-exposed asthmatics, compared with unexposed asthmatic subjects (49). In this study retrospective assessment of both ETS exposure and outcomes raises the question of potential recall bias. The

published epidemiologic studies suggest that ETS contributes both to development and exacerbation of asthma in adults, but definite conclusions cannot be reached because of a limited number of studies and potential problems in their design.

More relevant data are available from controlled exposure studies in asthmatic and healthy volunteers (44). The results have been quite inconsistent, probably because of different selection criteria of subjects, small study samples, and different exposure periods. However, there is evidence of a subgroup of asthmatics who are sensitive to ETS and respond to ETS exposure with symptoms, reduction in lung function, and increase in bronchial hyperresponsiveness. The determinants of this susceptibility are not known.

The available although limited literature on ETS in adults suggests that ETS may have a significant impact on exacerbation of asthma in adults, and further clinical and epidemiologic studies paying special attention to design issues are needed.

Low Birth Weight

For low birth weight, the charge for the workshop participants was to consider the full spectrum of the evidence on ETS and the growth of the fetus and to address the applicability of data from outside the workplace to pregnant women working outside the home.

Active smoking during pregnancy has been causally associated with reduced birth-weight. Misra and Nguyen (50) considered ETS exposure and reduced birth weight. For women of child-bearing age, the workplace is a particularly important locus of exposure. The literature on ETS exposure generally shows associations with adverse health effects including reduced birth weight. These findings were considered applicable in the workplace setting.

Concluding Remarks

This workshop addressed four outcome measures in relation to workplace exposure to ETS: lung cancer, ischemic heart disease, asthma, and low birth weight. The focus was on approaches for deriving quantitative risk estimates for workplace ETS exposure. In addition, cross-cutting issues were addressed including sources of bias that may have affected risk estimates and the use of meta-analysis and mathematical modeling for synthesis of the evidence. Although bias from confounding and exposure misclassification is a concern, the workshop participants found little evidence that estimates of ETS risk are substantially affected by bias.

For lung cancer, data from three types of studies are available that can be used to estimate risk related to ETS exposure: *a*) active smoking, particularly at lower levels of daily consumption, *b*) ETS exposure at home, and *c*) ETS exposure at work. Mathematical models for lung cancer risk from active smoking can be developed and then applied with extrapolation to ETS exposure levels. Estimates from studies of ETS exposure in the home can be extended to the workplace by considering the relative exposures in the two types of locations. Finally, several studies, particularly the large U.S. multicenter study (30), provide risk estimates based directly on reported workplace exposure.

For ischemic heart disease, there are now numerous reports of the increased risk associated with ETS exposure at home. Evidence is far more limited on ETS exposure at work. However, a meta-analysis approach was presented for estimating the hazard posed to workers by increased ischemic heart

disease risk from ETS exposure.

For asthma and low birth weight, only limited evidence on workplace exposure to ETS was available. Persons with asthma and pregnant women are groups considered susceptible to effects of inhaled pollutants in general. For children, ETS exposure at home is well characterized as exacerbating asthma and increasing medical morbidity. An effect of workplace exposure on adults with asthma is plausible, and experimental studies show that some asthmatics are sensitive to ETS. However, we need further investigation on workplace exposure to ETS as a risk factor for exacerbation of asthma.

Active smoking by the mother reduces infant birth weight, as does ETS exposure at home, although to a much lesser degree than active maternal smoking. On a biologic basis, ETS exposures at home and at work would be expected to have the same consequences for birth weight. Consequently, exposure of pregnant women to ETS in the workplace was considered an outcome of concern, while needing further investigation.

In combination, the two workshops--the 1997 workshop on exposure assessment and the 1998 workshop on health outcomes-- provide a framework for assessing the risks of ETS exposure in the workplace. An approach for assessment of ETS exposure was proposed in the 1997 workshop. The 1998 workshop added the needed complement of dose-response assessment for lung cancer and cardiovascular disease.

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